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# In The Supreme Court of the United States

WYETH,

*Petitioner,*

v.

DIANA LEVINE,

*Respondent.*

**On Writ Of Certiorari To The Supreme Court Of Vermont**

## BRIEF OF *NEW ENGLAND JOURNAL OF MEDICINE* EDITORS AND AUTHORS AS *AMICI CURIAE* IN SUPPORT OF RESPONDENT

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## INTEREST OF *AMICI CURIAE*

*Amici curiae*, all of whom hold degrees in medicine and related fields, are ten current and former editors and contributing authors of the New England Journal of Medicine ("NEJM"), including each editor-in-chief of NEJM since 1977.[1] NEJM is the oldest continuously published medical journal in the world, and has published numerous scholarly articles on, among other things, advances in drug therapy, prescription drug side effects, and the role of the United States Food and Drug Administration ("FDA") and the pharmaceutical industry in our health care system. For nearly 200 years, physicians have turned to NEJM as a source of important new information to guide their medical practice.

Beginning in the year 2000, *amici* **Jeffrey M. Drazen, M.D.**, and **Gregory D. Curfman**, **M.D.**, have served as NEJM's Editor-in-Chief and Executive Editor, respectively. Beginning in 2002, *amicus* **Stephen Morrissey, Ph.D.**, has served as Managing Editor of NEJM. Together, Drs. Drazen, Curfman, and Morrissey have more than 50 years of experience as editors.

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[1] Pursuant to Rule 37.6, *amici* state that no counsel for a party authored any part of this brief, and no person or entity, other than *amici* and their counsel, made any monetary contribution to the preparation or submission of this brief. Counsel of record for both parties have consented to the filing of this brief.

*Amicus* **Marcia Angell** served as NEJM's Executive Editor between 1988 and 1999 and as its Editor-in-Chief between 1999 and 2000. *Amicus* **Jerome P. Kassirer, M.D.**, currently Distinguished Professor at Tufts University School of Medicine, served as NEJM's Editor-in-Chief between 1991 and 1999, after which he was named Editor-in-Chief Emeritus. Between 1977 and 1991, *amicus* **Arnold S. Relman, M.D.**, served as NEJM's Editor-in-Chief, after which he became Editor-in-Chief Emeritus.

*Amicus* **Paul D. Stolley, M.D., M.P.H.**, former Professor and Chairman of the University of Maryland's Department of Epidemiology and Preventive Medicine and for five years a member of the FDA's Biometrics and Epidemiology Advisory Committee, served on NEJM's editorial board from 1989-1993, and has written 15 articles published in NEJM. *Amicus* **Harlan M. Krumholz, M.D., S.M.**, the Harold H. Hines, Jr. Professor of Medicine and Epidemiology and Public Health at Yale University School of Medicine and Editor-in-Chief of *Circulation: Cardiovascular Quality and Outcomes*, has authored 15 articles published in NEJM. *Amicus* **Stuart Rich**, **M.D.**, Professor of Medicine at the University of Chicago, has written six articles published in NEJM, including a study on the relationship between Pondimin/Redux and primary pulmonary hypertension. Finally, *amicus* **Eric J. Topol, M.D.**, the Founding Dean of the Scripps School of Medicine and Professor of Translational Genomics at The Scripps Research Institute, has written 35 articles published in NEJM.

The issue before this Court is one of immense importance from the perspective of public health and safety. *Amici*'s professional responsibilities have included evaluating the efficacy of prescription pharmaceutical drugs, the conduct of the pharmaceutical industry, and the ability of the FDA to ensure that safe and effective medications with adequate warnings are made available to American consumers and, when necessary, withdrawn from the marketplace. The matter under review by this Court – namely, whether federal law preempts failure-to-warn claims relating to prescription drugs – falls directly within *amici*'s professional responsibility to ensure that prescription drugs best serve the public's health. It is in performing that role that *amici* feel compelled to ask this Court to affirm the decision of the court below.

## SUMMARY OF ARGUMENT

The argument of Petitioner and its *amici* ("Petitioner/*Amici*") that federal preemption of state law failure-to-warn claims involving prescription drugs will actually make the world a safer place is riddled with factual fallacies. First, contrary to Petitioner's/*Amici*'s necessary premise, the FDA is in no position to ensure the safety of prescription drugs. Not only is the FDA seriously hampered in its ability to determine the risks of drugs before they are

approved for sale, but it has proven inadequate to the task of addressing hazards that only become apparent after a drug has been widely marketed to an unsuspecting public. Post-approval dangers posed by drugs placed into the market are unfortunately quite common. However, the FDA's ability to either anticipate these risks or react expeditiously once they have been revealed has been limited by serious information-gathering constraints in both pre- and post-approval settings.

Much of this stems from the fact that the FDA is heavily dependent on the drug makers themselves for the information on which the agency bases its decisions. Not surprisingly, this dependence has its drawbacks. Pharmaceutical companies at times learn about dangers caused by their drugs long before the FDA does, but have failed to disclose this information to the FDA. Thus, as exemplified by the cases of Pondimin/Redux, Vioxx, and Trasylol, the drug companies have withheld key information from the FDA and ardently negotiated against stricter label warnings – all the while continuing to market their unsafe drugs to an unsuspecting public. In the case of these three drugs alone, literally tens of thousands of American lives have been lost or ruined long after the manufacturers realized that the drugs were not safe.

In light of this sad reality, Petitioner's/*Amici*'s argument that failure-to-warn suits actually pose a danger to public health is nothing short of specious.

The theory that the risk of tort liability causes drug manufacturers to "over-warn" of the dangers of their drugs (thereby scaring patients away from drugs they need) not only has no empirical support, but it ignores the fact that *under*-warning has, unmistakably and tragically, exacted a terrible toll on public health and safety.

Equally specious are Petitioner's/*Amici*'s arguments that the $700 *billion* pharmaceutical industry, which grows more robust with every passing year, is somehow economically stifled by the products liability system. In arguing that immunity from failure-to-warn suits should uniquely be provided to their industry, they fail to consider that the tort system has played a crucial role in assisting the FDA in evaluating the benefits and risks of prescription drugs. As the examples of Pondimin/Redux, Vioxx, and Trasylol potently demonstrate, the FDA alone simply lacks the ability to serve as the sole guarantor of drug safety. Without the tort system, the FDA would be stripped of an essential source of information that the agency has consistently relied on when making its regulatory decisions, and the American public would be deprived of a vital deterrent against pharmaceutical company misconduct. Thus, rather than promote public health, the preemption of failure-to-warn claims would substantially *threaten* it. *Amici* therefore urge this Court to reject Petitioner's request for preemption.

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## ARGUMENT

### I. THE FDA LACKS SUFFICIENT INFORMATION AND RESOURCES TO SERVE AS THE SOLE MONITOR OF PHARMACEUTICAL RISKS

The position of Petitioner/*Amici* is that any product label approved by the FDA must necessarily constitute both the minimum and maximum that should be required. Their premise is that the FDA's function will be disrupted if it is not left alone to strike the proper balance between safety and efficacy. Product liability lawsuits, they argue, prevent the FDA from fulfilling its mission of ensuring that consumers receive optimal warning of the dangers of prescription drugs.

But for the FDA to strike that proper balance, it must be privy to all pertinent information regarding the benefits and risks of all prescription drugs. The FDA neither has nor could have the resources to perform this Herculean function, given the 11,000 FDA-regulated drugs on the market and the nearly one hundred more approved each year.[2] In fact, three

[2] *See* FDA Center for Drug Evaluation and Research, U.S. Dep't of Health and Human Servs. 2005 Report to the Nation: Improving Public Health Through Human Drugs 12 <http://www.fda.gov/cder/reports/rtn/2005/rtn2005.pdf>; FDA Science Board Report, *FDA Science and Mission at Risk* (2007) <http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf> ("FDA 2007").

recent analyses of the FDA's drug safety oversight – two by the Government Accountability Office ("GAO") and the other by the congressionally chartered National Academy of Science's Institute of Medicine ("IOM") – criticized the FDA's ability to keep unsafe drugs off the market and to respond effectively to observed hazards.[3] Many of these difficulties, however, are endemic to the FDA's system of acquiring information.

The FDA receives pre-market information regarding Adverse Drug Reactions ("ADRs") from clinical trials that are conducted by the drug companies themselves. While clinical trials represent an important aspect of drug development by providing efficacy assessments, their ability to assess a complete safety profile is inherently limited. *IOM Report* at 38. To demonstrate efficacy, studies generally range between a few hundred to 3000 subjects with a duration of from six to eight weeks to two years. These studies cannot fully account for: 1) the effects of long-term cumulative dose or latent ADRs; 2) rare ADRs or those most pronounced in sub-populations; or 3) potential ADRs not accounted for in clinical trial

[3] *See* U.S. Gov't Accountability Office, *Drug Safety: Improvement Needed in FDA's Post-market Decision-making and Oversight Process* <www.gao.gov/cgi-bin/getrpt?GAO-06-402> ("GAO 2006"); U.S. Gov't Accountability Office, *Drug Safety: FDA's Oversight of the Promotion of Drugs for Off-Label Uses* <http://www.gao.gov/new.items/d08835.pdf>; Institute of Med. of the National Academy of Science, *The Future of Drug Safety* (Baciu, Alina, *et al.*, eds., 2006) ("*IOM Report*").

designs. In addition, for ethical reasons studies are often conducted on "lower-risk" rather than "higher-risk" populations.

Given that the FDA conducts no independent testing, the information it relies on is necessarily provided by the party most interested in bringing the drug to market – the drug manufacturer. Even under the best of circumstances, the FDA often lacks the ability of those conducting a study to interpret the data generated. FDA 2007 at 31. Moreover, the FDA's own Science Board found that the FDA lacks sufficient expertise in quantitative methods, such as statistics and biomathematics, to effectively assess products and guide sponsors to design valid and informative studies. *Id*. at 35. As a result of these weaknesses, manufacturers, rather than the FDA, are often the first to learn of serious ADRs related to their drugs, while the FDA is wholly reliant upon their reporting. The system's limitations have been confirmed by one early analysis by the GAO, which concluded that 51.5 percent of all approved drugs had at least one serious ADR not recognized before approval.[4]

Post-approval evaluation of drug risks has not cured the serious defects in the pre-approval process. Although the FDA generally requires companies

[4] U.S. Gov't Accountability Office, *Drug Safety: Post-Approval Risks 1975-1986* at 3 <http://archive.gao.gov/d24t8/141456.pdf>.

marketing new drugs to perform post-approval or "Phase IV" studies,[5] these studies until very recently have been almost completely out of the FDA's control.[6] Historically, the FDA has lacked the authority to require such studies, GAO 2006 at 5, to grant conditional approval for drugs requiring further study, or to conduct direct legal action in this regard. Indeed, FDA action against a drug company for failing to submit clinical study information virtually never occurs. Given this lack of regulatory consequences, in 2003, the estimated post-market study completion rate was only 24 percent. GAO 2006 at 28. An FDA report that checked unsatisfied commitments as of September 2005 found that of 1,231, almost two-thirds (797) were "pending," *i.e.* not even initiated, with just 21 percent listed as "ongoing" or "delayed."

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[5] Tufts Ctr. for the Study of Drug Dev., "FDA Requested Post-marketing Studies in 73% of Recent New Drug Approvals," *Impact Report*, July-Aug. 2004, <http://csdd.tufts.edu/_documents/www/Doc_309_42_893.pdf>.

[6] The FDA Amendments Act of 2007 tries to address this problem by giving the agency authority to require Phase IV studies for "serious risk[s]" and to set timetables for study completion. FDAAA, tit. IX, sec. 901(a), § 505(o)(3)(B-E), 121 Stat. 823, 923-924. As explained in the *amicus curiae brief* of AARP, these amendments will only have a very limited ability to enhance the FDA's goal of addressing post-approval risks.

Many of the so-called "pending" study commitments even lacked a completion deadline.[7]

The FDA also attempts to monitor post-approval performance by gathering reports of ADRs through its Adverse Event Reporting System and "MedWatch" program. 21 C.F.R. § 310.305 (2006). While this is indeed a critical system for data-gathering, by the FDA's own estimate "it hears of less than 1 percent of serious adverse reactions."[8] Even to the extent information is received, drug companies are often in a better position to distinguish between drug-induced and naturally occurring events. Just receiving ADRs at times can be of limited utility, because the FDA often will not know how many people use a given drug in order to calculate the incidence of any adverse reaction.[9] These weaknesses contribute to the FDA's difficulty in promptly identifying serious, less common, ADRs, making it even more dependent on

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[7] *See* Report on the Performance of Drug and Biologics Firms in Conducting Post-Marketing Commitment Studies, 71 Fed. Reg. 10978-79 (2006).

[8] Reauthorization of the PDUFA: Hearing Before the Subcommittee on Health of the H. Comm. on Energy and Commerce, 107th Cong. 49 (2002) (statement of Rep. Henry A. Waxman) <http://energycommerce.house.gov/reparchives/107/action/107-93.pdf>; *See* also *IOM Report* at 53 (reporting that the 400,000 reports received each year represent only a "small fraction of all adverse effects of drugs.").

[9] *See* Steenburg, "*The Food and Drug Administration's Use of Post-Marketing (Phase IV) Study Requirements: Exception to the Rule?*" 61 Food & Drug L.J. 295, 298, n.30. (2006).

pharmaceutical companies to share complete information.

## II. THE FDA'S LIMITATIONS AS THE SOLE MONITOR OF PHARMACEUTICAL RISKS ARE ILLUSTRATED BY DRUGS THAT HAD TO BE WITHDRAWN FOR SAFETY REASONS

There can be little argument regarding the risk/benefit calculus for drugs withdrawn due to safety concerns – by definition their initial warnings proved inadequate. As shown in Appendix "A," drugs requiring complete withdrawal from the market for safety reasons are not rare.[10] While drug withdrawals are the ultimate protection for public safety, withdrawals are also the most extreme remedy that can be taken by the FDA. Withdrawal is often the result of an assessment that can take years to develop, as is demonstrated by the length of time between approval and withdrawal for many of the drugs listed in Appendix "A." The FDA has many options before complete withdrawal. For one, heightened warnings, including "black box" warnings, can be given for a

[10] *See, e.g.,* Wysocki, *et al.*, "*Adverse Drug Event Surveillance and Drug Withdrawals in the United States, 1969-2002,*" 165 Arch. Int. Med. 1363 (2005); 21 C.F.R. § 215; "List of Drug Products that have been Withdrawn or Removed from the Market for Reasons of Safety or Effectiveness" <http://www.fda.gov/ohrms/dockets/98fr/100898b.txt>; FDA CDER, Report to the Nation: 2005 <http://www.fda.gov/CDER/reports/rtn/2005/rtn2005-4.htm>.

drug. A pharmaceutical company may even unilaterally add new warnings to their drugs, subject to subsequent FDA approval. *See Osburn v. Anchor Labs., Inc.*, 825 F.2d 908, 913 (5th Cir. 1987) (discussing 21 C.F.R. § 314.70).[11]

Often, withdrawals occur only after lengthy negotiations between the FDA and manufacturers over appropriate warnings. Indeed, although the majority of drug withdrawals eventually occur worldwide, the FDA as a result has at times been comparatively slow to act. (*See*, *e.g.,* trovafloxacin, suspended in Europe in 1997, but not until 2000 in the U.S., and troglitazone ("Trovan"), withdrawn from the U.K. in 1997, but not suspended until 2000 in the U.S.). This delay can be compounded when manufacturers actively withhold critical information from the FDA in order to delay the implementation or severity of warnings, as was the case with Redux/Pondimin, Vioxx, and Trasylol, discussed below.

In the examples of Redux/Pondimin and Vioxx, discovery conducted during the course of product liability litigation has revealed that the pharmaceutical companies were aware of serious ADRs long before the FDA, but that they failed to provide information to the FDA even while patients were being

[11] While Petitioner/*Amici* might argue that 21 C.F.R. § 314.70 is limited to "new" evidence, such a reading would not comport with the scientific process. Scientific information is acquired over time with "older" information informing "new" information until a new conclusion is drawn.

injured.[12] As a result, tens of thousands of patients were unnecessarily exposed to potentially life-threatening conditions. These examples demonstrate that the FDA, heavily reliant upon industry-supplied data, cannot reasonably be expected to be the sole guarantor of the nation's drug safety.[13]

### A. Fenfluramine/Dexfenfluramine (Pondimin/ Redux)

Fenfluramine, marketed as Pondimin by American Home Products ("AHP," currently known as "Wyeth"), was an anti-obesity drug that was approved by the FDA in 1973 for short-term use. Dexfenfluramine, containing one of Pondimin's two molecules, was marketed by AHP beginning in June 1996 as "Redux." In September 1997, years after its risks became known, both drugs were finally withdrawn from the market because they were linked to two very serious conditions: valvular heart disease and primary pulmonary hypertension ("PPH"). *See* 64 Fed. Reg. 10944-01 (1999), 21 C.F.R. § 216.24 (1999).

PPH is a rare, disabling, and usually fatal disease that occurs in the general population at the rate

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[12] *See* Curtin, Draven & Morrissey, *et al.*, "*Preamble Preemption and the Challenged Role of Failure to Warn and Defective Design Pharmaceutical Cases in Revealing Scientific Fraud, Marketing Mischief, and Conflicts of Interest,*" 35 Hofstra Law Rev. 1773 at 1782-83 (2007) (listing examples).

[13] *See* Curfman, *et al.*, "*Why Doctors Should Worry about Preemption*," NEJM, 359:1 (2008).

of only one or two per million. Fenfluramine's link to PPH was referenced in the scientific literature as early as the 1970's[14] and was certainly known to occur by 1981.[15] Moreover, in December 1993, French pulmonologist Francois Brenot published an article, entitled "Primary Pulmonary Hypertension and Fenfluramine Use," that surveyed fenfluramine-related PPH prior "case reports" in the medical literature. Plotting 73 cases observed and confirmed in various European clinics, Brenot found that fifteen patients, or twenty percent, had ingested fenfluramine.[16]

However, ADRs for fenfluramine-related PPH prior to 1992 were rare, because sales of Pondimin were not significant. This began to change in 1992 when a series of articles related to an AHP-supported study by Dr. Michael Weintraub appeared in the Journal of Clinical Pharmacology and Therapy. These advocated the use of fenfluramine in combination with the generic drug phentermine to achieve weight loss without the adverse effects of fenfluramine

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[14] *See* Buczko, "*Effect of Fenfluramine on 5-Hydroxytryptamin Uptake and Release*," British J. Pharmacol., 53(4): 633-38 (1975); Seiler, *et al*., "*On the Role of Serotonin and the Pathogenesis of Pulmonary Hypertension*," Clinical Experimental Pharmacology, Physiology, 3(4): 323-30 (1976).

[15] Douglas, *et al.,* "*Pulmonary Hypertension and Fenfluramine,*" 6296 Brit. Med. J. 881-83 (1981).

[16] Brenot, *et al.*, "*Primary Pulmonary Hypertension and Fenfluramine Use*," Br. Heart J., Vol. 70(6) 537-541 (Dec. 1993).

mono-therapy. This regimen popularly became known as "Fen-Phen." Between 1993 and 1997, sales of Pondimin, the "fen" in fen-phen, rose exponentially.[17]

Between late 1994 and early 1995, AHP acquired American Cyanamid and the rights to bring dexfenfluramine (Redux) to market. Predictions indicated that Redux would create sales of $1 billion in its first three years on the market, depending upon whether or not there would have to be significant warnings about PPH. With so much at stake in gaining Redux's approval by the FDA, AHP chose not to inform the FDA that it was aware of ten times more Pondimin-related PPH cases than were listed on the Pondimin product label.[18]

Virtually any scientific doubt regarding PPH causation ended in March 1995 upon presentation of the interim results of an epidemiologic study sponsored by Servier, AHP's recently acquired partner in the distribution of dexfenfluramine. This study linked fenfluramine to PPH, showing that diagnosis was

[17] Salbu, "*Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*," 51 FLLR 181, 203 (April 1999).

[18] Avorn, *Powerful Medicines*, New York: Random House (2004) at 74-75.

nine times more likely in those exposed at all to the drug.[19]

Nevertheless, AHP's package insert and Physician's Desk Reference entry for Pondimin between January 1989 and December 1996 continued to mention just four reported cases of PPH in which only one person died. Moreover, this was the only Pondimin "warning" regarding PPH that AHP provided to the medical community or American public between 1989 and late 1996. The "warning" section of the Pondimin product label itself was silent about PPH.

Instead of sending out a "Dear Doctor" letter or moving to change its warnings in response to the study and ADRs it was accumulating on PPH, AHP spent its resources fighting the requirement that it include a "black box" warning regarding PPH on its

[19] The "IPPHS" study was a prospective case-controlled human epidemiological study conducted in 35 centers in Europe. Abenhaim, *et al.*, "*Appetite Suppressant Drugs and the Risk of Primary Pulmonary Hypertension*," 335 NEJM 609-16 (Aug. 29, 1996). Ninety-five patients with pulmonary hypertension were compared with 355 control subjects. When appetite suppressants were used for greater than three months, the study demonstrated a 23-fold increased risk of developing pulmonary hypertension. The authors concluded that the evidence indicated that appetite suppressants caused pulmonary hypertension. *See also* Rich, *et al.*, "*Anorexigens and Pulmonary Hypertension in the United States: Results from the Surveillance of North American Pulmonary Hypertension,*" 117 CHEST 871 (Mar. 2000).

packaging[20] – even though internally AHP circulated a "death listing report" to keep track of the number of Pondimin consumers dying from PPH.[21] Nevertheless, it was not until July 1996, that a draft label revision was finally submitted to the FDA, and January 1997 that AHP's first "Dear Health Care Professional" letter was sent to American physicians.

In July 1997, AHP disclosed to the FDA that a cluster of fen-phen related valvular heart disease cases had been reported and analyzed by the Mayo Clinic in March 1997. These cases revealed valvular heart disease in patients taking fen-phen.[22] It was subsequently learned that AHP had been receiving dozens of reports of heart valvulopathy since the

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[20] *See In Re: DIET DRUGS (Phentermine, Fenfluramine, Dexfenfluramine) Products Liability Litigation*, 2003 WL 22023361 at 8 (E.D.Pa. 2003) (Exhibit P-78: November 22, 1995 Memo re: Dexfenfluramine Assessment states on bates stamped page AHP-Q-00013941: "[e]very attempt will be made to ensure that no 'Black Box' Warnings, restrictions of use or negative statements find their way into the Redux labeling.") Shortly thereafter, Wyeth V.P. JoAlene Dolan was able to write: "The meeting with FDA yesterday was a tremendous success! No black box." Mundy, Dispensing with the Truth, New York: St. Martin's Griffin (2001) at 52.

[21] Mundy, "Pillow-boxed In," *Washington Monthly*, Oct. 2003 <http://findarticles.com/p/articles/mi_m1316/is_10_35/ai_n27677094>.

[22] Connolly, *et al.*, "*Valvular Heart Disease Associated with Fenfluramine-Phentermine,*" 337 NEJM 581-88 (1997). (Twenty-four women who had used fenfluramine (some for less than three months) had developed heart valve disease diagnosed by echocardiogram.)

early 1990's though they were never reported to the FDA.[23]

While AHP was receiving this dire news regarding the adverse health impacts of Redux and Pondimin, both drugs were proving to be economic blockbusters. In 1996 alone, one million people used Redux while six million used Pondimin. Also in 1996, over eighteen million prescriptions for fen-phen were filled in the United States.[24] Tragically, this marketing success was directly proportional to the grave health consequences of AHP's diet drugs. If one assumes the accuracy of IPPHS's conclusion that "the absolute risk is estimated to be 100 cases of PPH per million users," then in 1996 alone, 700 people contracted generally fatal PPH in exchange for at best minor, temporary weight loss.

### B. Rofecoxib (Vioxx)

Rofecoxib, marketed under the name Vioxx, was one of a new breed of nonsteroidal anti-inflammatory drugs (NSAIDs) – COX-2 inhibitors – that were designed to compete with the extremely profitable and growing market of nonselective anti-inflammatory

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[23] *See In Re: Diet Drugs (Phentermine/Fenfluramine/Dexfenfluramine) Products Liability Litigation*, 369 F.3d 293 (3rd Cir. 2004).

[24] McGrath, "*Only a Matter of Time: Lessons Unlearned at the Food And Drug Administration Keep Americans at Risk*," Food and Drug Law Journal, 60 Food DLJ 603, 616 (2005); Salbu, *supra*, at 203.

drugs, such as Naproxen (Aleve) and Ibuprofen. Once approved by the FDA on May 19, 1999, Vioxx quickly became one of the most successful drugs in pharmaceutical history, averaging over two billion dollars in sales per year,[25] with total sales from 1999 through 2004 exceeding ten *billion* dollars. But just five years after its introduction, on September 30, 2004, Vioxx was withdrawn from the market due to cardiovascular problems resulting in heart attacks, strokes, and death.

The likelihood that Vioxx would cause cardiovascular problems was known to Merck not only well before 2004 but also before its 1999 release date. In 1997, a clinical trial revealed that Vioxx resulted in systemic reduction of a critical component to the human body's defense mechanism against heart attacks, prostacyclin.[26] Nevertheless, before Vioxx was released, Merck failed to test the potential for Vioxx to cause cardiovascular problems.[27]

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[25] Johnson, "Merck Agrees to Blanket Settlement on Vioxx," Washington Post, Nov. 10, 2007 <http://www.washingtonpost.com/wp-dyn/content/article/2007/11/09/ARZ00711.html

[26] *See* Catella-Larson, *et al.*, "Selective Inhibition of Cyclooxygenase II in the Elderly: Effects on Sodium Balance, Hemodynamics, and Vasoactive Eicosanoids" <http://www.vioxxdocuments.com/Documents/Krumholz_Vioxx/Morrison1998.pdf>.

[27] *See* Psaty, *et al.*, "*COX-2 Inhibitors – Lessons in Drug Safety,*" 352 NEJM 1133, 1134 (2005).

Thus, when Vioxx was first approved for sale in 1999, its label contained no meaningful warning describing a risk of adverse cardiovascular events, such as heart attacks and strokes.[28] Nor was there a Phase-IV plan in place for Merck to conduct a study assessing these risks. Instead, Merck chose to conduct an 8,000 patient trial, called "VIGOR," with the hope of furthering Vioxx's sales at the expense of competing Naproxen. Merck hoped that the trial would aid sales by demonstrating that Vioxx resulted in fewer gastrointestinal problems than Naproxen, these being a known side-effect of most NSAIDs. Instead, early results of the study showed that patients taking Vioxx experienced four times the number of heart attacks (the final results revised this to five times the number of heart attacks) than patients taking Naproxen. In an internal memo dated March 9, 2000, Merck Research Laboratories' President Dr. Edward Scolnick, wrote: "The CV [cardiovascular] events are clearly there . . . [T]his is real . . . " *McDarby*, *supra* at 14.

Eighteen days after receiving these results linking Vioxx to heart attacks, Merck issued a press release attributing the difference in the incidence of heart attacks in the VIGOR study to an alleged

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[28] Merck & Co., Inc., Vioxx (Rofecoxib Tablets and Oral Suspension) label, NDA 21-042 <http://www.fda.gov/cder/foi/nda/99/021042_52_vioxx_prntlbl.pdf>.

cardio-protective effect of naproxen.[29] Merck put forward this theory despite being told by its own expert consultants that they had no clinical evidence that naproxen was cardio-protective. *McDarby, supra* at 30. Nevertheless, this naproxen explanation was disseminated to the public and the medical community through numerous press releases, direct mailings to physicians, and Merck-sponsored publications in medical journals. Notably absent from these promotions was any mention that Vioxx might have caused serious ADRs.[30]

In October 2001, the FDA proposed that Vioxx carry a warning for cardiovascular events in its label. Merck refused. No pertinent labeling change was made until April 2002 when Merck finally amended the label to include, at the FDA's insistence, a "precaution" though only for those patients with a history of cardiovascular events.[31]

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[29] *McDarby, supra* at 29-30. (Merck also stressed in this release the gastrointestinal safety of Vioxx.).

[30] *Id. See also* Krumholz, *et al.*, "*What Have We Learnt From Vioxx?*" BMJ 2007; 334: 120-123.

[31] *McDarby, supra* at 45 ("Merck proposed relocation of the FDA's text to the Precautions section of the label, and to modify the text to de-emphasize the risk of Vioxx"); *Id.* at 47-48 ("The revised label for Vioxx was approved on April 11, 2002, two years after the results of the VIGOR study were known, and a 'Dear Doctor' letter substantially incorporating the information set forth in the label was circulated by Merck that same month. A review of the label demonstrates that Merck successfully obtained the FDA's consent to use of a revised label that contained no

(Continued on following page)

At about this time, two other studies, Protocols 078 and 091, also demonstrated a three-to-four times increased risk of mortality for patients taking Vioxx when compared with those taking a placebo.[32] When Merck first learned of these results, it was in the midst of negotiating a new label for Vioxx with the FDA. *Id.* Despite ongoing discussions with the FDA, Merck never gave these analyses to the FDA nor did it disclose any of this information to the medical community or patients. *See* Psaty, *supra.*

Meanwhile, when promoting Vioxx to physicians, Merck sales representatives were taught to "dodge" doctors' questions about the cardiovascular risks of the drug.[33] If the VIGOR study was brought up, they were instructed to show physicians a "Cardiovascular

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mention of cardiovascular risks in the "Warnings" section, but instead, contained a "Precaution" that limited use of Vioxx only among patients "with a medical history of ischemic heart disease" – patients whose already-diagnosed coronary artery disease was symptomatic." The label did note that: "Prospective studies specifically designed to compare the incidence of serious CV events in patients taking Vioxx versus NSAID comparators or placebo have not been performed.").

[32] *See* Memorandum, Apr. 8, 2001: "MK0955 Combined Mortality Analysis Protocol 091 + Protocol 078," at 6-7 <http://www.biostat.washington.edu/research/Rofecoxib/Ref%2014%20-%20Merck%20Statistician%20Alzheimer's%20Mortality%20Report.pdf>

[33] *McDarby*, *supra* at 40. ("Dodge Ball Vioxx" documents instructed sales representatives how to "dodge" obstacles that included questions about Vioxx's risk.).

Card," but not leave it with the physician. *McDarby, supra*, at 40. This card compiled data from selected studies on Vioxx that purported to demonstrate a favorable cardiovascular and mortality profile for Vioxx.[34]

At the same time, Merck either authored and/or sponsored publications in medical journals that provided misleading safety profiles for Vioxx.[35] Advocates were paid by Merck to give lectures to other doctors about Vioxx. The FDA cited some of these lectures as containing false and misleading promotions concerning the safety and efficacy of Vioxx. *McDarby*, *supra*, at 42-43.

On September 30, 2004, Merck finally withdrew Vioxx from the market after still another clinical trial, APPROVe, demonstrated a more than two-fold risk of heart attack and other cardiovascular adverse events in patients taking Vioxx as compared with a placebo.[36] During the five years Vioxx was on the

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[34] Merck & Co., Inc., "In Response To Your Questions – Once Daily Vioxx (refecoxib): Cardiovascular System – Clinical Profile in Osteoarthritis Studies" <http://www.vioxxdocuments.com/Documents/Krumholz_Vioxx/Merck2000CVcard.pdf>.

[35] *See* Krumholz, *supra*, at 120; *also see* Ross, *et al.*, *Guest Authorship and Ghostwriting in Publications Related to Rofecoxib,* JAMA 2008, 299(15): 1800-1812.

[36] Bresalier, "*Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial*," NEJM, 352: 1092-1102 (2005) and annexed *Correction*, <http://content.nejm.org/cgi/reprint/352/11/1092.pdf>.

market, over 100 million prescriptions were written for an estimated 20 million patients.[37] Applying the risk-levels seen in VIGOR and APPROVe, it has been estimated that between 88,000 and 139,000 Americans suffered Vioxx induced cardiovascular events, of whom 30-40 percent (24,000-55,600) died.[38]

### C. Aprotinin (Trasylol)

Bayer Pharmaceuticals began marketing Trasylol in the 1970s. In 1987, Dr. David Royston discovered that Trasylol would reduce blood loss and the need for transfusions in repeat heart bypass surgery.[39] In December, 1993, the FDA approved Trasylol for prophylactic use during these surgeries. Fifteen years later, Trasylol was withdrawn from the market for causing kidney failure, resultant dialysis, and death.

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[37] *See In Re: Vioxx Prods. Liab. Litig*., 501 F. Supp. 2d 776, 779 (E.D. La. 2007).

[38] *See* Graham, M.D., M.P.H., Testimony to United States Senate Committee on Finance, Nov. 18, 2004. <http://finance.senate.gov/hearings/testimony/2004test/111804dgtest.pdf>. Another estimate is that up to 320,000 cases of heart attacks and strokes occurred due to Vioxx. Topol, "*Failing the Public Health – Rofecoxib, Merck, and the FDA*," NEJM, 351: 1707-1709 (Oct. 21, 2004) ("Given the finding in the colon-polyp trial in low-risk patients without known cardiovascular disease – an excess of 16 myocardial infarctions or strokes per 1000 patients – there may be tens of thousands of patients who have had major adverse events attributable to rofecoxib.")

[39] Royston, *et al*., "*Effect of aprotinin on need for blood transfusion after repeat open-heart surgery,*" Lancet, 1987; ii: 1289-1291.

Before gaining approval for Trasylol, Bayer had ample warning signs regarding Trasylol's effect on kidney function. Early 1980's toxicological studies indicated Trasylol was not easily broken down by the kidneys, while other studies demonstrated severe kidney damage in test animals.[40] In 1992, a year before Trasylol was approved by the FDA, a study found that, of 20 patients administered Trasylol, 13 reported problems with kidney function.[41] Despite this information, only a minority of the 45 Trasylol clinical studies conducted prior to the FDA's approval even commented on renal function. Of these, none had sufficient numbers of patients to determine whether Trasylol exposure increased the risk of renal failure.

In August 1998, as a condition for approving amendments to the Trasylol Package Insert regarding non-kidney-related ADRs, the FDA required Bayer to conduct post-approval clinical studies, along with evaluations and analyses, as a condition for its

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[40] Fisher, *et al.*, "*High-dosage Aprotinin (Trasylol) Therapy – Is It Safe For The Kidney?*" Langenbecks Arch. Chir. 1983; 360(4): 241-9.; Fisher, *et al.*, "*Aprotinin (Trasylol) Protection – Unsuitable for Hypothermic Kidney Preservation,*" Transplantation, 1984 37(1): 115.

[41] Sundt, *et al.*, "*Renal dysfunction and intravascular coagulation with aprotinin and hypothermic circulatory arrest,*" Ann. Thorac. Surg., July 1993, 55: 1418-1424.

approval of the revised Package Insert.[42] Bayer did not conduct the clinical studies required by the FDA, nor did it conduct any evaluations or analyses that would generate clinically meaningful information about the safety of Trasylol. Between August 1998 and December 2006, no material safety information was reviewed by the FDA for inclusion in the Trasylol Package Insert.[43]

In 2006, *NEJM* published an article by Dr. Dennis Mangano that specifically analyzed the relationship between Trasylol administration and kidney failure. Mangano's study closely followed a study by Dr. Keyvan Karkouti that compared Trasylol with a competitor, tranexamic acid, and found the two were equally effective, but that only Trasylol had a significantly negative effect on renal function.[44] The Mangano study reported that study patients who were given Trasylol were more than twice as likely to have kidney failure requiring dialysis, had 55 percent more heart failures, and 181 percent more strokes. The authors advised against further use of Trasylol,

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[42] *See* FDA Center for Drug Evaluation and Research, Approval Package & Final Printed Labeling for Aprotinin <http://www.fda.gov/cder/foi/nda/98/020304s004_appltr_prntlbl.pdf>.

[43] *See* FDA Center for Drug Evaluation and Research, Approval History for Aprotinin: NDA 020304 <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist>.

[44] Karkouti, *et al*., "*A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery*," Transfusion, 2006, 46, 3: 327-338.

because safer, cheaper drug alternatives were available.[45]

On February 1, 2006, Bayer commissioned an external study to be done by i3 Drug Safety ("i3"), hoping to contradict Mangano's work. For the next eight months, Bayer kept the existence of its commissioned study by i3 secret from the public and the FDA.

In May 2006, the FDA announced that in September 2006 it would convene a meeting of its Cardiovascular and Renal Drugs Advisory Committee. The FDA asked Bayer to submit information relevant to Trasylol and specifically to address the issues raised by the Mangano and Karkouti studies. Bayer submitted voluminous information to the FDA and contacted the agency several times regarding the Trasylol meeting, but failed to disclose its commission of the i3 study.

A week before the meeting, i3 and its principal investigator Dr. Alexander Walker released the preliminary findings of their study to Bayer. The i3 study examined the medical records of approximately 67,000 patients, of whom 30,000 received Trasylol. It confirmed the findings of Karkouti and Mangano.[46]

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[45] Mangano, *et al.*, "*Risks Associated with Trasylol in Cardiac Surgery,*" NEJM, 2006, 354(4):353-65.

[46] FDA Center for Drug Evaluation and Research, Transcript of Cardiovascular and Renal Drugs Advisory Committee In Joint Session With The Drug Safety and Risk Management Advisory

(Continued on following page)

On September 21, 2006, the FDA held an Advisory Committee Meeting to discuss the safety and overall risk-benefit profile for Trasylol. After multiple presentations on the safety and efficacy of Trasylol by Bayer – again without any mention of the i3 study – the FDA Committee voted that there should be no changes to the Trasylol labeling.[47]

In response to Bayer's failure to disclose the i3 study to the FDA, Dr. Walker revealed the details and outcome of the study to the agency. The study demonstrated that Trasylol may increase the chance for death, serious kidney damage, congestive heart failure, and strokes. *Id*. Two days later, the FDA issued a second safety alert regarding the use of Trasylol and Bayer's failure to disclose the i3 study.[48] The FDA warned physicians to carefully monitor patients for the occurrence of toxicity, particularly to the kidneys, heart, or brain, and promptly report ADRs.

Finally, on December 15, 2006, that the FDA required that the Package Insert for Trasylol include additional Warnings and Precautions.[49] The FDA also

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Committee, September 12, 2007 at 22-23 <http://www.fda.gov/ohrms/dockets/AC/07/transcripts/2007-4316t1-part1.pdf>.

[47] *See* Zuckerman Spaeder LLP, "Report on Trasylol for Bayer Corporation and Bayer AG," (Aug. 1997) <http://pharma.bayer.com/html/pdf/BAYER_REPORT_FINAL_8-2007.PDF>.

[48] FDA, "Statement regarding new Trasylol data" <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01472.html>.

[49] *See* FDA Approval History, *supra*.

finally sent out an alert to healthcare professionals, advising them of a change in the product label for Trasylol and stating: "[T]he new label has a more focused indication for use, a new Warning about renal dysfunction, a revised Warning about anaphylactic reactions, and a new Contraindication."[50]

In June 2007, the University of Connecticut published a study, known as the REACTS study, which showed findings almost identical to those shown in Mangano's study.[51] On November 5, 2007, a Canadian-based clinical study, known as the BART study, was released to the public. The BART study was halted in October 2007 due to an alarming death rate associated with Trasylol. The BART study showed an increased risk of death when compared with aminocaproic acid and tranexamic acid, consistent with the findings in other studies that safer, cheaper, and equally effective alternatives for Trasylol existed.[52] After the findings of the BART study were published, the FDA could not identify any specific patient population as to which it believed the

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[50] FDA, *Information for Healthcare Professionals* <http://www.fda.gov/CDER/Drug/InfoSheets/HCP/aprotininHCP.pdf>.

[51] Coleman, *et al.*, "*Evaluating the safety implications of aprotinin use: The Retrospective Evaluation of Aprotinin in Cardio Thoracic Surgery (REACTS)*," J. Thorac. Cardiovasc. Surg. 2007, 133: 1547-1552.

[52] Fergusson, *et al.*, "*A comparison of aprotinin and lysine analogues in high-risk cardiac surgery,*" NEJM, 358(22): 2319-2331 (2008).

benefit of using Trasylol outweighed the risks. On May 15, 2008, years after first becoming aware of the risks of Trasylol, Bayer suspended worldwide sales of Trasylol following an FDA request to remove the drug from the market for safety reasons.

Between 1999 and 2005, Bayer generated over $935 million in revenue from sales of Trasylol with over $353 million in 2005.[53] Bayer forecast that Trasylol would some day generate upwards of $600 million annually. In February 2008, on the CBS program *60 Minutes*, Dr. Mangano estimated that, of the 431,000 people who took the drug after he published his analysis, 22,000 lives could have been saved.[54] While the true number of those who died as a result of Trasylol administration will never be known, given Bayer's own estimate that, through 2005, 4.3 million patients had been given Trasylol, it is possible that another 220,000 died as a result of using Bayer's product.

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[53] *See* Bayer Annual Reports (Form 20-F) (converted from euros on Aug. 6, 2008) <http://sec.gov/Archives/edgar/data/1144145/000115697302000306/f00360e20vf.txt>; <http://sec.gov/Archives/edgar/data/1144145/000132693206000060/0001326932-06-000060-index.htm>; and <http://sec.gov/Archives/edgar/data/1144145/000115697303000973/f00582e20vf.htm>.

[54] "One Thousand Lives A Month," *60 Minutes*, CBS, Feb. 17, 2008, <http://www.cbsnews.com/stories/2008/02/14/60minutes/main3831900.shtml>.

## III. PETITIONER'S POLICY ARGUMENTS IN FAVOR OF PREEMPTION LACK ANY EMPIRICAL BASIS

The discussions above related to Pondimin/Redux, Vioxx, and Trasylol demonstrate the extent to which pharmaceutical manufacturers have delayed necessary warnings when substantial profits are at risk. The import of this is rather striking in light of Petitioner's/*Amici*'s two major arguments in support of preemption: that the true risks and benefits of prescription drugs will be obscured by too many warnings ("over-warning") and that product liability litigation has adversely affected the economics of the pharmaceutical industry and its ability to provide drugs that are needed. Neither is true.

### A. The Risk of "Over-warning" is More Theoretical Than Real

Petitioner's/*Amici*'s primary policy justification for preemption is that litigation forces manufacturers to add unnecessary warnings, which allegedly confuse both patients, who stop using necessary drugs, and medical practitioners, who fail to prescribe optimal drug therapies. Petitioner/*Amici* also maintain that drug manufacturers will be punished by the FDA adding unnecessary warnings in response to failure-to-warn lawsuits. Notably, however, despite seventy years of drug regulation by the FDA, neither Petitioner nor

its *amici* cite to a single example where a drug manufacturer was punished for over-warning.[55]

Nor is there any evidence that "overwarning" has resulted in underutilization of prescription drugs. While Petitioner/*Amici* (*see*, *e.g.,* WLF at 14-15) cite to studies where pharmaceutical therapies might have underutilized, the cited references do not attribute the underutilization to "over-warnings" added in response to product liability lawsuits.

Nor have Petitioner/*Amici* provided any evidence that medical professionals would be better off with fewer warnings. In advancing this argument, Petitioner/*Amici* ignore the fact that prescription drug labeling is directed to a sophisticated physician audience that is well able to comprehend a thorough product insert. Medical practitioners have consistently requested complete warnings, albeit formatted in a user-friendly fashion.[56]

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[55] *See* Nagareda, "*FDA Preemption: When Tort Law Meets the Administrative State,*" J. Tort L. art. 4 at 32, n. 127, citing *McNellis v. Pfizer, Inc.*, No. Civ. 05-1286 (JBS), 2005 WL 3752269 (D. N.J. 2005), *rev'd on other grounds, Colacicco v. Apotex Inc.*, 521 F.3d 253 (3rd Cir. 2008) (noting submission of former FDA official's affidavit asserting lack of awareness of any instance in which the agency had deemed misbranded a drug whose labeling included additional statements beyond those required as part of FDA approval).

[56] PhRMA at 15 cites to a national survey of physicians described at 65 Fed. Reg. 81,082-84. The complaints referenced did not go to "over-warning" but rather formatting for ease of use.

In fact, close scrutiny of Petitioner/*Amici*'s briefing reveals a lack of even putative instances where "over-warning" affected prescription drug usage. Their examples include: 1) warnings not required by the tort system but by the FDA itself regarding the consumption of fish (WLF at 17-19); 2) third generation birth control pills that were challenged not by the tort system but by the consumer group Public Citizen in a petition to the FDA (WLF at 20-22); and 3) a controversy over vaccinations sparked not by a lawsuit but by an article spread through the popular press (PhRMA at 23-24).[57] Even if "over-warning" were truly a problem with respect to drug underutilization, these examples demonstrate that lawsuits play only a minor role at best in fueling the public's perceptions.

Indeed, in over 400 pages of briefing, Petitioner/*Amici*'s pharmaceutical "over-warning" examples reference just one class of drugs, SSRIs, and two individual drugs, Norplant for birth control, and Bendectin. Even in the case of the drug most frequently mentioned, Bendectin,[58] the alleged lack of a replacement therapy speaks primarily to the small market for drugs designed to alleviate non-severe

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[57] Virtually all vaccine cases are heard in "vaccine court" pursuant to the no-fault provisions of The National Childhood Vaccination Injury Act rather than through the civil justice system. *See* National Childhood Vaccination Injury Act, 42 U.S.C. § 300aa-1, *et seq*.

[58] *See* Calfee at 15; DRI at 31-32; PhRMA at 23-24.

"morning sickness" (severe "morning sickness," *hyperemesis gravidarum*, requires hospitalization). Moreover, in contrast to the withdrawn drugs discussed at length above, Petitioner/*Amici* do not point to a single article that states that the failure to use Bendectin caused any long-term damage to either a mother or her fetus.

Furthermore, it is extraordinary that Petitioner/*Amici* would repeatedly return to Bendectin as their best example of "over-warning" justifying preemption when this Court has already opined in a Bendectin case regarding the appropriate manner in which courts should evaluate the merits of pharmaceutical failure-to-warn cases. *See Daubert v. Merrell-Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993). There, this Court mandated judicial scrutiny over the necessary pharmacological, toxicological, and often epidemiological expert testimony required to meet the evidentiary requirements for medical and scientific causation related to the condition requiring a warning in drug-related injury cases. *See also General Electric Co. v. Joiner*, 552 U.S. 136 (1997)[59]; *Weisgram v. Marley*, 528 U.S. 440, 442 (2000) ("Since *Daubert* . . . parties relying on expert evidence have had notice of the exacting standards of reliability such evidence

[59] NEJM has previously stated that this is the appropriate screening mechanism for meritorious claims. *See* "Brief *amici curiae* of the New England Journal of Medicine and Marcia Angell, M.D., in support of neither petitioners nor respondents" filed in *Joiner*, *supra*.

must meet.") Twenty-eight states, including Vermont, now apply *Daubert* or a similar test, six apply *Daubert* factors, and all states have some mechanism for scrutinizing the admissibility of scientific evidence before it is presented to a jury. 90 ALR 5th 453.[60] To argue that warnings are being required for random "unsubstantiated" outcomes ignores fifteen years of post-*Daubert* jurisprudence.[61]

### B. Petitioner's/*Amici*'s Economic Arguments for Preemption Are Little More Than a General Indictment of the Entire Product Liability System

All of Petitioner's/*Amici*'s principal economic policy arguments in favor of federal preemption are routinely made by manufacturers of all products: *i.e.*, that subjecting manufacturers to tort liability creates a risk of over-deterrence that might result in excessive risk control, stifle innovation, and impose unreasonable costs, including subjecting them to the costs of liability defense and insurance. In making these time-worn arguments, Petitioner/*Amici* do not supply any

[60] *Daubert* has led all state and federal courts to increase their scrutiny over such scientific evidence regardless of the standard applied. *See* Cheng, *et al.*, "*Does Frye or Daubert Matter?*" 91 Va. L. Rev. 471 (2005).

[61] Note that PhRMA at 7, n.2, excises a pre-*Daubert* quote from 1979.

empirical evidence to explain why the pharmaceutical industry uniquely deserves such blanket protection.[62]

The prescription drug industry earns global revenues of more than $700 billion per year, an increase of $178 billion over the last five years.[63] Petitioner/*Amici*'s argument that tort suits have led Americans to underutilize prescription drugs or companies to limit product development is baseless. As of 2004, Americans were responsible for $248 *billion* in pharmaceutical sales, accounting for nearly 45 percent of all revenue worldwide.[64] Despite representations of a so-called explosion of stifling litigation, the pharmaceutical market has grown, not shrunk. And it has done so dramatically: In 2007 alone, there were approximately 445 million more prescriptions written than in 2003.[65]

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[62] Notably, their economic-based arguments are not based upon preemption, as all of these arguments would be precisely the same if the FDA didn't exist.

[63] IMS Health, "IMS Health Reports Global Prescription Sales Grew 6.4 Percent in 2007, to $712 Billion," April 16, 2008 <http://www.imshealth.com/portal/site/imshealth/menuitem.fc2127a7c34504dc88f611019418c22a/?vgnextoid=38bd4822d7699110VgnVCM10000071812ca2RCRD&vgnextchannel=41a67900b55a5110VgnVCM10000071812ca2RCRD&vgnextfmt=default>.

[64] IMS Health, "IMS Reports 2004 Global Pharmaceutical Sales Grew 7 Percent to $550 Billion," Mar. 9, 2005 <http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_71496463,00.html>.

[65] *See* IMS Health, 2007 Channel Distribution by U.S. Dispensed Prescriptions <http://www.imshealth.com/deployedfiles/ims

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Meanwhile, liability costs referenced by Petitioner/*Amici* pale in comparison to promotional costs. Drug companies now spend over $29 billion annually just to promote their products, including $11.4 billion on advertising.[66] Nothing demonstrates this better than the case of Vioxx. In 2000, Vioxx was the number one direct-to-consumer advertised drug at $160 million – larger than the campaigns that year for Pepsi and Budweiser.[67]

## IV. UNDER THIS COUNTRY'S REGULATORY FRAMEWORK, EFFECTIVE MONITORING OF DRUG RISKS REQUIRES A ROBUST TORT SYSTEM

Product liability lawsuits and the FDA have peacefully coexisted for seventy years for one simple reason: they have complementary, rather than conflicting, goals. The tort system complements the federal regulatory structure by providing a mechanism for compensating victims of hazardous drugs. Product liability litigation provides the FDA with key information unearthed in litigation that the agency can use to better protect the public from unsafe and

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health/Global/Content/Document/Top-Line%20Industry%20Data/2007%20Channel%20Distribution%20by%20RXs.pdf>.

[66] Donohue, *et al.*, *"A Decade of Direct-to-Consumer Advertising of Prescription Drugs,"* 357 NEJM 673, 674 (2007).

[67] Nat'l Inst. for Health Care Mgmt., *Prescription Drugs and Mass Media Advertising*, 2000, at 5 (2001) <http://www.nihcm.org/~nihcmor/pdf/DTCbrief2001.pdf>.

inadequately labeled drugs. At the same time, the tort system and the FDA are similarly constrained. Whereas the FDA, as a regulatory body, weighs the risks against the benefits of a drug, in "failure-to-warn" litigation most state courts require a similar balancing between the cost of care owed to a patient versus the prospective harm.[68] As former FDA chief counsel Margaret Porter wrote, "FDA product approval and state tort liability usually operate independently, each providing a significant, yet distinct, layer of consumer protection."[69]

Frequently, serious safety issues come to light only after a drug has entered the market. However, the FDA, unlike most other federal agencies, has no subpoena power and, therefore, only knows what a manufacturer chooses to reveal to it. Companies have no obligation to provide the FDA with internal company evaluations of a drug's performance in the

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[68] Judge Learned Hand described his formula in *United States v. Carroll Towing Co.,* 159 F.2d 169, 173, *reh'g denied*, 160 F.2d 482 (2d Cir. 1947), where he compared the cost of precautions with the expected loss. *See* Gilles, "*On Determining Negligence: Hand Formula Balancing, The Reasonable Person Standard, and the Jury,*" 54 Vand. L. Rev. 813, 816-22 (2001) (describing the broad use, as well as complications, in applying Hand's formula).

[69] Porter, "*The Lohr Decision: FDA Perspective and Position,*" 52 Food & Drug L.J. 7, 9 (1997).

market, let alone the company's internal documents frankly assessing a drug's safety profile.[70]

By contrast, state tort law provides essential information-gathering tools, which can be an important avenue by which the health care community learns of safety and efficacy information.[71] Through the process of discovery, litigation has regularly uncovered information about drug toxicity that would otherwise not have been known, such as the type discussed above in the cases of Pondimin/Redux and Vioxx. Discovery in both instances revealed that the companies knew much more about their product's safety problems than they ever revealed to the FDA, the medical profession, or the public.

Secondly, by levying damages for certain kinds of harm, tort law can provide powerful disincentives to risky behaviors, as well as aid the FDA in its mission. In these days of budget cutbacks, with declining resources to pay for inspections, investigations, and legal actions, the products liability system becomes a vital element in promoting compliance with the FDA's safety goals. Even the threat of civil liability is a vital bargaining tool for the FDA in pressuring companies

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[70] *See* Kesselheim, *et al.*, "*The Role of Litigation in Defining Drug Risks,*" 297 JAMA 308, 310 (2007).

[71] *See* Struve, "*The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation,*" 5 Yale J. Health Policy & Ethics 587, 591 (2005) (noting preemption removes opportunity for litigation system to aid in effort to monitor product safety).

to amend labels to warn of newly understood risks. If pharmaceutical companies were granted almost complete immunity by virtue of federal preemption, they would have minimal incentive to report or warn of the adverse health effects of their drugs. In fact, given that pharmaceutical companies have been known to equate increased warnings with a loss of sales, they would have an incentive to delay warnings as long as possible. As has been shown, certain pharmaceutical companies have already proven themselves unwilling to prioritize safety over profits, even when faced with the threat of civil liability.[72] It is chilling to imagine how such companies might conduct themselves if the threat of tort liability for dangerous drugs were eliminated entirely by virtue of federal preemption.

Finally, the civil justice system has the ability to improve the lives of injured patients and their families in ways that the FDA cannot. It can provide protection in cases like the examples of Trasylol and Vioxx, where the FDA was late in acting. Meritorious lawsuits can transfer the obligation to pay for the losses caused by tragic ADRs from this country's

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[72] *See* Davis, "*The Battle over Implied Preemption: Products Liability and the FDA,*" 48 B.C. L. Rev. 1089, 1095 (2007); O'Steen, "*The FDA Defense: Vioxx® and the Argument Against Federal Preemption of State Claims for Injuries Resulting from Defective Drugs,*" 48 Ariz. L. Rev. 67, 96 (2006); Schwartz, "*Regulatory Standards and Products Liability: Striking the Right Balance Between the Two,*" 30 U. Mich. J.L. Rev. 431 (1997).

healthcare system to pharmaceutical companies. As written so bluntly by FDA counsel Porter, the tort system remedies the "harsh implications" of the FDA's inability to provide "recourse for consumers injured by defective" drugs. Porter, *supra* at 9.

## CONCLUSION

Because the preemption of state failure-to-warn claims involving prescription drugs would threaten this nation's public health by eliminating a necessary counterpart to the FDA, *Amici* urge this Court to affirm the decision of the court below.

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**APPENDIX "A"**

| TRADEMARK NAME | MARKET NAME | PURPOSE | FIRST SOLD | WITH-DRAWN | REASON WITHDRAWN |
|---|---|---|---|---|---|
| Amineptine | Survector | anti-depressant | 1978 | 1999 | hepatoxicity |
| Aprotinin | Trasylol | heart bypass bleeding reduction | 1993 (for use) | 2007 | kidney damage; death |
| Astemizole | Hismanal | edema and antihistamine | 1988 | 1999 | fatal heart problems |
| Azaribine | Triazure | severe arthritis | 1975 | 1977 | embolisms |
| Benoxaprofen | Oraflex | anti-inflammatory | 1982 | 1982 | cholestatic jaundice; death |
| Bromfenac | Duract | pain | 1997 | 1998 | liver failure |
| Butamben | Efocaine | local anesthetic | 1952 | 1964 | paraplegia |
| Cerivastatin | Baycol | cholesterol reduction | 1997 | 2001 | rhabdomyolysis; death |
| Chlorma-dinone acetate | Estalor-21, C-Quens | oral contraceptive | 1965 | 1972 | emboli |
| Cisapride | Propulsid | gastro-esophageal reflux | 1993 | 2000 | arrhythmias; death |
| Dexfen-fluramine | Redux | appetite suppressant | 1996 | 1997 | pph; cardiac valvulopathy |
| Diamthazole dihydro-chloride | Asterol | antifungal agent | 1951 | 1977 | neurotoxicity |
| Diethylstil-bestrol (DES) | Stilpho strol, etc. | multiple – most vaginally related | 1941 | tablets 1975; gradually limited | birth defects; vaginal adeno-carcinoma in daughters |
| Encainide | Enkaid | arrhythmia | 1986 | 1991 | increased risk of death from arrhythmia |

| TRADEMARK NAME | MARKET NAME | PURPOSE | FIRST SOLD | WITH-DRAWN | REASON WITHDRAWN |
|---|---|---|---|---|---|
| Etretinate | Tigason | psoriasis | 1985 | 1998 | high risk of birth defects |
| Fenfluramine | Pondimin | appetite suppressant | 1973 | 1997 | PPH; cardiac valvulpathy |
| Flosequinan | Manoplax | congestive heart failure | 1992 | 1993 | increased hospitalization; death |
| Grepafloxacin | Raxar | pneumonia; bronchitis | 1997 | 1999 | arrhythmia; death |
| Hydro-morphone | Palladone | analgesia; cough suppressant | 2004 | 2005 | fatal when taken with alcohol |
| Levomethadyl | Orlaam | opiate addiction | 1995 | 2004 | cardiac arrest |
| Nomifensine | Merital | anti-depressant | 1985 | 1986 | kidney/liver toxicity; death |
| Pergolide Mesylate | Permax | Parkinson's symptoms | 1988 | 2007 | heart valvulopathy |
| Mepazine | Pacatal | anesthesia | 1955 | 1970 | seizures; intestinal paralysis; |
| Mibefradil | Posicor | hypertension; chronic angina | 1997 | 1998 | congestive heart failure |
| Oxyphenisatin | Laverna, etc. | laxative | 1955 | 1973 | liver failure |
| Pemoline | Cylert | ADHD and narcolepsy | 1975 | 2005 | liver failure |
| Phenformin hydrochloride | Fenormin | Type-2 diabetes | 1959 | 1977 | fatal lactic acidosis |
| Pipamazine | Mornidine | vomiting; nausea | 1959 | 1969 | kidney lesions |
| Rapacuronium | Raplon | anesthesia | 1999 | 2001 | respiratory spasms; death |

| TRADE-MARK | MARKET NAME | PURPOSE | FIRST SOLD | WITH-DRAWN | REASON WITHDRAWN |
|---|---|---|---|---|---|
| Reserpine | Reserpoid, Rau-Sed | hypertension | 1954 | 1977 | irregular heartbeat; hearing loss; vision problems |
| Rofecoxib | Vioxx | pain; arthritis | 1999 | 2004 | heart attack; stroke; death |
| Sulfadi-methoxine | Madri-cidin | respiratory infections | 1959 | 1966 | Stevens-Johnson syndrome |
| Sulfathiazole | Tresamide | antimicrobial | 1939 | 1970 | kidney and liver damage; death |
| Suprofen | Suprol | anti-inflammatory | 1985 | 1987 | kidney toxicity |
| Technetium fanolesomab | Neutro-Spec | diagnosing appendicitis | 2004 | 2005 | cardiopulmonary failure; death |
| Tegaserod Maleate | Zelnorm | irritable bowel; constipation | 2002 | 2007 | serious heart problems |
| Temafloxacin | Omniflox | infections | 1992 | 1992 | anemia; death |
| Terfenadine | Seldane | antihistamine | 1985 | 1998 | fatal arrhythmia |
| Thalidomide | Multiple | sedative -- hypnotic | 1956 | 1962 (re-stricted) | severe limb birth defects |
| Tienilic Acid | Ticrynafen | anti-hypertensive | 1979 | 1980 | kidney failure; liver toxicity |
| Troglitazone | Rezulin | Type-II diabetes | 1997 | 2000 | liver toxicity |
| Trovafloxacin | Trovan | serious infection | 1997 | 1998 (re-stricted) | liver toxicity |
| Urethane | Profenil | muscle relaxant | 1976 | 1977 | carcinogenicity |
| Valdecoxib | Bextra | arthritis, etc. | 2001 | 2005 | Stevens Johnson syndrome; heart attack |
| Zomepirac | Zomax | pain | 1981 | 1983 | fatal and near fatal anaphylactic reactions |